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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,920	TOWNSEND ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *11,13-16,20-27 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,17-19,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group I (claims 1-10, 12, 17-19 and 28-29) in the reply filed on 9/20/04 is acknowledged.

The request for corrected filing receipt filed on 9/20/04 is acknowledged. A corrected filing receipt will be mailed to Applicants.

Claims 1-30 are pending in the present application.

Claims 11, 13-16, 20-27 and 30 are withdrawn from further consideration because they are drawn to non-elected inventions.

Claims 1-10, 12, 17-19 and 28-29, drawn to a method for increasing the production of clavulanic acid in a host and a method for increasing the production of N2-(2-carboxyethyl)arginine in a host cell by gene dosing, and a host cell stably transformed with *orf2*, are examined on the merits herein.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 9-10, 12, 17-19 and 28-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's elected invention is drawn to a method for increasing the production of clavulanic acid in a host comprising the step of increasing the level of N^2-(2-carboxyethyl)arginine synthase in a host by any gene dosing including the use of any DNA encoding said N^2-(2-carboxyethyl)arginine synthase, wherein the N^2-(2-carboxyethyl)arginine synthase catalyzes the condensation of L-arginine and D-glyceraldehyde-3-phosphate (claims 1-5, 7, 9-10 and 12). Applicants' elected invention is also directed to a method for increasing the production of N^2-(2-carboxyethyl)arginine in a host cell via enhancing the rate of condensation of L-arginine and D-glyceraldehyde-3-phostphate by increasing the copy number of any gene encoding N^2-(2-carboxyethyl)arginine synthase (claims 17-19); and a host cell stably transformed with any *orf2* gene (claims 28-29).

However, apart from the disclosure of the *orf2* gene encoding N^2-(2-carboxyethyl)arginine synthase from the clavulanic acid biosynthetic pathway in *Streptomyces clavuligerus*, the instant specification fails to describe structural characteristics of any other genes or any other nucleotide sequences (naturally

occurring and/or non-naturally occurring sequences) that encode N^2-(2-carboxyethyl)arginine synthase or mediate the unprecedented condensation of L-arginine with D-glyceraldyde-3-phosphate to yield N^2-(2-carboxyethyl)arginine. The instant specification also fails to provide a representative number of species for a broad genus of a DNA or a gene or *orf2* encoding N^2-(2-carboxyethyl)arginine synthase to be utilized in the methods and to make a host cell as claimed by the present application.

At about the effective filing date of the present application (9/16/1999), apart from the disclosed *orf2* gene encoding N^2-(2-carboxyethyl)arginine synthase from the clavulanic acid gene cluster in *Streptomyces clavuligerus* (Jensen et al., US Patent 6,232,106; Hodgson et al., US Patent 5,759,831), virtually nothing was known about the structure or characteristics of the *orf2* gene encoding N^2-(2-carboxyethyl)arginine synthase from other *Streptomyces* species, let alone from any other biological sources.

The claimed invention as a whole is not adequately described. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). Apart from the *orf2* gene encoding N^2-(2-carboxyethyl)arginine synthase from the clavulanic acid gene cluster in *Streptomyces clavuligerus*, the skilled artisan cannot envision the detailed structure of a broad genus of a DNA or a gene or *orf2* encoding N^2-(2-carboxyethyl)arginine synthase (an essential component) to be utilized in the methods and to make a host cell as claimed by the present application; and therefore

conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 9-10, 12, 17-19 and 28-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1. A method for increasing the production of clavulanic acid in a *Streptomyces* host that is capable of carrying out the biosynthesis of clavulanic acid, said method comprises the step of:

increasing the level of N^2-(2-carboxyethyl)arginine synthase in said host by providing the host with a DNA sequence encoding N^2-(2-carboxyethyl)arginine synthase

obtained from *Streptomyces clavuligerus*, wherein said N^2-(2-carboxyethyl)arginine synthase catalyzes the condensation of L-arginine and D-glyceraldehyde-3-phosphate, resulting in increased production of clavulanic acid;

2. A method for increasing the production of N^2-(2-carboxyethyl)arginine in a *Streptomyces* host cell that is capable of carrying out the biosynthesis of clavulanic acid, said method comprises the step of:

enhancing a rate of condensation of L-arginine and D-glyceraldehyde-3-phosphate in said host by increasing a copy number of the *orf2* gene encoding N^2-(2-carboxyethyl)arginine synthase obtained from *Streptomyces clavuligerus* in said host, wherein said step of enhancing results in an increase in the production of N^2-(2-carboxyethyl)arginine in said host cell; and

3. A host cell stably transformed with *orf2* gene encoding N^2-(2-carboxyethyl)arginine synthase obtained from *Streptomyces clavuligerus;*

does not reasonably provide enablement for a method for increasing the production of clavulanic acid or a method of increasing the production of N^2-(2-carboxyethyl)arginine in <u>any other host or host cells using any other DNA or gene encoding N^2-(2-carboxyethyl)arginine synthase or a host cell stably transformed with any other *orf2* genes</u>. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction

or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, the specification teaches by exemplification showing that the *orf2* gene from the clavulanic acid gene cluster in *Streptomyces clavuligerus* mediates the unprecedented condensation of L-arginine with D-glyceraldehyde-3-phosphate to yield N^2-(2-carboxyethyl)arginine (example 1). Additionally, Applicants teach the cloning of the *orf2* gene into a replicating plasmid as well as various integrative vectors, and that expression of the additional *orf2* gene in *S. clavuligerus* results in an enhancement of clavulanic acid production (examples 2-4).

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the present broadly claimed invention for the following reasons.

1. The breadth of the claims

With respect to the elected invention, claims 1-5, 7, 9-10, 12 are drawn to a method for increasing the production of clavulanic acid in any host (e.g., *E. Coli*, any plant or animal host) comprising the step of increasing the level of N^2-(2-carboxyethyl)arginine synthase in a host by any gene dosing including the use of any DNA encoding said N^2-(2-carboxyethyl)arginine synthase, wherein the N^2-(2-carboxyethyl)arginine synthase catalyzes the condensation of L-arginine and D-glyceraldehyde-3-phosphate (claims 1-5, 7, 9-10 and 12). Claims 17-19 are directed to

a method for increasing the production of N^2-(2-carboxyethyl)arginine in any host cell by increasing the copy number of any gene encoding N^2-(2-carboxyethyl)arginine synthase. When read in light of the specification, the sole purpose for a method of increasing the production of N^2-(2-carboxyethyl)arginine in a host cell is for the production of clavulanic acid (see specification, page 1, lines 8-14; page 5, lines 4-9; page 10, lines 18-22); otherwise there is no other disclosed uses for the production of N^2-(2-carboxyethyl)arginine in a host cell. Claims 28-29 are drawn to a host cell stably transformed with any *orf2* gene. It is noted that a host cell stably transformed with *orf2* can be used in an assay for the identification of potential substrates of N^2-(2-carboxyethyl)arginine synthase (see specification, page 9, lines 19-29).

2. The state and unpredictability of the prior art

At the effective filing date of the present application (09/16/1999), apart from *Streptomyces clavuligerus*, *Streptomyces jumonjinensis* ATCC 29864 and *Streptomyces katsurahamanus* T-272 bacteria which are known to be natural producers of clavulanic acid, little was known whether other hosts are also capable of producing clavulanic acid, particularly the pathway and complete essential genes required for clavulanic acid biosynthesis have not been clearly established (Hodgson et al., US Patent 5,759,831; Jensen et al., US 6,232,106). Although Jensen et al (US 6,232,106) have shown that clavulanic acid can be produced in *Streptomyces lividans* strains that have been transformed with an 11.6 kb fragment containing a cluster of genes (including the *orf2* gene) obtained from the genome of *Streptomyces clavuligerus*, the prior art at the effective filing date of the present application did not teach that other

heterologous hosts such as any other bacteria, yeasts, plant or animal cells are also capable of producing clavulanic acid as long as they contain the same 11.6 kb fragment, let alone of any host containing only a DNA encoding N^2-(2-carboxyethyl)arginine synthase. Moreover, the physiological art has also been recognized as unpredictable (MPEP 2164.03).

3. The amount of direction or guidance provided

Apart from the exemplification showing the expression of the additional *orf2* gene obtained from *S. clavuligerus* results in an enhancement of clavulanic acid production in *S. clavuligerus*, the instant specification fails to provide sufficient guidance for a skilled artisan on how to increase the production of clavulanic acid or increasing the production of N^2-(2-carboxyethyl)arginine for the production of clavulanic acid in any other hosts such as any other *non-Streptomyces* bacteria, plant or animal hosts by providing said hosts with any DNA encoding N^2-(2-carboxyethyl)arginine synthase. Since the prior art at the effective filing date of the present application did not provide such guidance, it is incumbent upon the present application to do so. In light of the totality of the prior art as discussed above, coupled with the lack of sufficient guidance provided by the present disclosure it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

As the claims also encompass the utilization of any DNA or any gene encoding N^2-(2-carboxyethyl)arginine synthase or *orf2* gene, including and not limited to one encoding the enzyme having amino acid substitutions, insertions, deletions, truncations (see instant specification, page 5, lines 10-16) in the methods and a transformed host

cell as claimed, the instant specification fails to teach which encoded amino acid(s) to be substituted, deleted or inserted, at which positions and in which combinations such that the DNA or gene encoding any N^2-(2-carboxyethyl)arginine synthase is still capable of enhancing a rate of condensation of L-arginine and D-glyceraldehyde-3-phosphate. Nor does the instant specification teach any other *orf2* genes encoding N^2-(2-carboxyethyl)arginine synthase obtained from other sources apart from the *orf2* gene of *Streptomyces clavuligerus*. In discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstaking experimental study (Page 6, first sentence of Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). Furthermore, the relationship between the sequence of a peptide and its tertiary structure associated for its activity, is neither well understood nor is it predictable (Ngo et al., *In* Merz et al., ed. "The protein folding problem and tertiary structure prediction", Birkhauser, 1994). Thus, in light of the state of the prior art at the effective filing date of the present application and given the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make an use the instant broadly claimed invention.

Furthermore, with regard to the breadth of a method for increasing the production of clavulanic acid in any host or for increasing the production of N^2-(2-carboxyethyl)arginine synthase in any host cell using any DNA or gene encoding N^2-(2-carboxyethyl)arginine synthase and a host cell stably transformed with any *orf2* gene,

Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

4. Working example provided

Apart from the exemplification showing the expression of the additional *orf2* gene obtained from *S. clavuligerus* results in an enhancement of clavulanic acid production in *S. clavuligerus*, the instant specification fails to provide any other examples indicating that increased production of clavulanic acid or increased production of N^2-(2-carboxyethyl)arginine synthase could be attained in any other host or host cells using any other DNA or gene encoding N^2-(2-carboxyethyl)arginine synthase. The specification also fails to provide examples of host cells stably transformed with any other *orf2* gene other than the *orf2* gene obtained from *S. clavuligerus.*

In summary, due to the lack of sufficient guidance provided by the specification regarding to specific issues raised above, the unpredictability of the physiological art, the breadth of the claims, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Claims 6 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6 and 8 are directed to a method for increasing the production of clavulanic acid in any host comprising the step of providing said host the replicating plasmid pKC1139/pro-orf2-ter or the step of integrating into the chromosome of said host an integrative vector selected from the group consisting of pSET152/pro-orf2, pSET152/ermE(XbaI)-orf2 and pSET152/ermE(HindIII)-orf2, respectively.

In addition to the enablement issue on the increasing production of clavulanic acid in any host set forth above, the application discloses the replicating plasmid pKC1139/pro-orf2-ter and the integrative vectors pSET152/pro-orf2, pSET152/ermE(XbaI)-orf2 and pSET152/ermE(HindIII)-orf2 that are encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that these biological materials are essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether these biological materials are known and readily available to the public or that the written instructions are sufficient to reproducibly construct this

biological material from starting materials known and readily available to the public. Particularly, Applicants obtained the cloning vectors pKC1139, pSET152 from C.R. Hutchison (University of Wisconsin, Madison, WI) rather from a commercial source, and that pL8, a genomic library clone containing clavulanic acid gene cluster, is obtained from the Department of Chemistry of The John Hopkins University. Accordingly, availability of such biological materials is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the limitation "said constitutive promoter is *ermE**" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because in claim 3 from which claim 10 is dependent, there is no recitation of constitutive promoter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 9, 12, 17-19 and 28-29 are rejected under 35 U.S.C. 102(e) as being anticipated by Jensen et al. (US 6,232,106).

Jensen et al disclose an isolated 15 kb genomic DNA fragment from *Streptomyces clavuligerus* which encodes 10 ORFs, and within this 15 kb DNA lies an 11.6 kb *EcoRI* fragment which codes for eight proteins (ORF2 to ORF9) and enables

the production of clavulanic acid by *Streptomyces lividans* transformants (col. 1, lines 59-67; col. 6, lines 6-34; Figures 2-3; SEQ ID Nos 15 and 4). Jensen et al teaches specifically that the 11.6 kb fragment contains all the necessary genetic information for clavulanic acid production in *Streptomyces lividans*. Jensen et al further teach that clavulanate production by *S. clavuligerus* may be modified by introduction of extra copies of the gene or genes for rate limiting enzymes or by alteration of the regulatory components controlling expression of the genes for the clavulanate pathway (col. 4, lines 42-50). ORF2, ORF3, ORF6, ORF8 and ORF9 are apparently essential gene products for the production of clavulanic acid in *Streptomyces lividans* (see effect of mutations within the ORF's of the 11.6 kb fragment discussed below). Additionally, introduction of the 11.6 kb DNA sequence in *Streptomyces lividans* strains which do not normally produce clavulanate results in clavulanic acid production (col. 4, lines 51-59) as well as in other suitable hosts such as *S. parvulus*, *S. griseofulvus*, *S. antibioticus* and *S. lipmanii*. Suitable vectors to be used include pIJ702, pJOE829 and pIJ922 (col. 4, lines 60-63). Moreover, Jensen et al teach that the DNA sequences of their invention enable the production of one or more of the enzymes of the clavulanate pathway by expression of the relevant gene or genes in a heterologous expression system (col. 4, lines 64-67). Example 4 shows that the 11.6 kb EcoR1 was cloned into a bifunctional plasmid that is capable of replicating in either *E. coli* or in *S. lividans* (col. 10, lines 30-36), and thiostrepton resistant *S. lividans* transfomants (stable transformants because they are selected under the presence of thiostrepton, and please note that this is an exemplification because Jensen et al also teach that clavulanate production by *S.*

clavuligerus may be modified by introduction of extra copies of the gene or genes for rate limiting enzymes in the same manner and that ORF2, ORF3, ORF6, ORF8 or ORF9 are essential for clavulanic acid production) were assayed for evidence of clavulanic acid production (col. 10, lines 45-67). Jensen et al also teach transformants containing mutants with insertion in any one of the ORF2, ORF3, ORF6, ORF8 or ORF9 failed to produce beta-lactamase inhibitory activity of clavulanic acid, indicating that each of these ORFs are involved in the production of clavulanic acid (col. 13, lines 3-34). The nucleotide sequence between the partial ORF1 and the complete ORF2 in the 11.6 kb EcoR1 fragment contains the endogenous promoter/enhancer regulatory sequence of the ORF2; and its endogenous promoter is apparently a constitutive promoter because ORF2 expression is not required any inducer and that ORF2 expression is required for the production of clavulanic acid as already noted above (see example 4 and example 6).

As the method taught by Jensen et al contains the same step (increasing a gene copy number) and the same essential material (ORF2 gene as that of the present invention) as the claimed methods, it is inherent that the level of N^2-(2-carboxyethyl)arginine synthase as well as the rate of condensation of L-arginine and D-glyceraldehyde-3-phospate in the exemplified *S. lividans* transformants are also enhanced.

Accordingly, the teachings of Jensen et al meet all the limitation of the instant claims. Therefore, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al. (US 6,232,106) in view of Hodgson et al. (US Patent No. 5,759,831).

The claims are drawn to a method for increasing the production of clavulanic acid in a host comprising the step of increasing the level of N^2-(2-carboxyethyl)arginine synthase in a host, wherein said N^2-(2-carboxyethyl)arginine synthase catalyzes the condensation of L-arginine and D-glyceraldehyde-3-phosphate, resulting in increased production of clavulanic acid and said increasing step is performed by integrating a DNA encoding said N^2-(2-carboxyethyl)arginine synthase into the chromosome into said host.

Jensen et al disclose an isolated 15 kb genomic DNA fragment from *Streptomyces clavuligerus* which encodes 10 ORFs, and within this 15 kb DNA lies an 11.6 kb *EcoRI* fragment which codes for eight proteins (ORF2 to ORF9) and enables the production of clavulanic acid by *Streptomyces lividans* transformants (col. 1, lines 59-67; col. 6, lines 6-34; Figures 2-3; SEQ ID Nos 15 and 4). Jensen et al teaches specifically that the 11.6 kb fragment contains all the necessary genetic information for clavulanic acid production in *Streptomyces lividans*. Jensen et al further teach that clavulanate production by *S. clavuligerus* may be modified by introduction of extra copies of the gene or genes for rate limiting enzymes or by alteration of the regulatory components controlling expression of the genes for the clavulanate pathway (col. 4, lines 42-50). Additionally, introduction of the 11.6 kb DNA sequence in *Streptomyces lividans* strains which do not normally produce clavulanate results in clavulanic acid production (col. 4, lines 51-59) as well as in other suitable hosts such as *S. parvulus*, *S. griseofulvus*, *S. antibioticus* and *S. lipmanii*. Suitable vectors to be used include pIJ702, pJOE829 and pIJ922 (col. 4, lines 60-63). Example 4 shows that the 11.6 kb EcoR1 was cloned into a bifunctional plasmid that is capable of replicating in either *E. coli* or in *S. lividans* (col. 10, lines 30-36), and thiostrepton resistant *S. lividans* transformants were assayed for evidence of clavulanic acid production (col. 10, lines 45-67).

Jensen et al do not specifically teach to integrate the 11.6 kb EcoR1 into the chromosome of *S. lividans* or other suitable hosts such as *S. parvulus*, *S. griseofulvus*, *S. antibioticus* and *S. lipmanii* for the production of clavulanic acid.

However, at the effective filing date of the present application Hodgson et al already teach that DNA sequence comprising one or more genes encoding one or more enzymes involved in the biosynthesis of clavulanic acid in the form of a vector capable of transforming and undergoing autonomous replication in a clavulanic-acid producing organism or a vector from which insert DNA can be integrated into the chromosome of clavulanic acid producing organism via homologous recombination (see abstract and col. 3, lines 9-18).

Accordingly, at the effective filing date of the present application it would have been obvious for an ordinary skilled artisan to modify the method taught by Jensen et al. by integrating the 11.6 kb EcoR1 into the chromosome of *S. lividans* or suitable hosts such as *S. parvulus*, *S. griseofulvus*, *S. antibioticus* and *S. lipmanii* for the production of clavulanic acid in light of the teachings of Hodgson et al.

An ordinary artisan would have been motivated to carry out the above modification to produce more stable or permanent transformants or *Streptomyces* strains by integrating the 11.6 kb EcoR1 containing genes that are essential for the clavulanic acid production into the chromosomes of *S. lividans, S. parvulus*, *S. griseofulvus*, *S. antibioticus* and *S. lipmanii* for the production of clavulanic acid.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Jensen et al., and Hodgson et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Quang Nguyen, Ph.D.

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address. (See 37 C.F.R. § 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent. (See 37 C.F.R. § 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. (See 37 C.F.R. § 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 C.F.R. § 1.806).

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.